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The Beryllium Granuloma

Beryllium disease may exist as two main entities, acute and chronic. The acute form, nonspecific chemical pneumonitis, was first described by Weber & Englehardt (1933) and the chronic form by Hardy & Tabershaw (1946) under the name granulomatous pneumonitis. Occasionally (Freiman & Hardy 1970), the acute disease progresses to the chronic variety. Most cases result from inhalation exposure and thus primarily affect the lungs. It must be stressed, however, that the condition is a systemic disease and affects other organs: skin, eyes, nose, heart, bones, liver and kidneys. Beryllium disease may also affect the skin alone (Tepper *et al.* 1961). Hypersensitivity plays an important role and there is often a disparity between the concentration of beryllium in the tissue and the severity of the disease, and frequently a latent interval between exposure and onset. Skin reactions to beryllium salts are common and individual susceptibility is prominent.

The majority of the early cases followed exposure to beryllium phosphors used in fluorescent lamps but since 1948 these compounds have not been used. Beryllium, however, is increasingly used in a large variety of industries (Table 1) and therefore continues to be an industrial hazard.

The reported American and some British cases have been catalogued by Hardy (1955, 1963) and the pathological features of their series have been recently analysed (Freiman & Hardy 1970). Jones Williams (1958) listed 6 cases in the British literature and 16 have now been reported (Rogers 1957, Jordan & Darke 1958, Sneddon 1958, Wood *et al.* 1958, Sita-Lumsden 1959, McCallum *et al.* 1961, Norris & Peard 1963, Jones Williams *et al.* 1967).

The length of exposure prior to development of the disease may be anything up to 23 years. The duration of the disease is often over ten years and the fatality rate about 35% (Stoeckle *et al.* 1969).

The criteria for diagnosis include known exposure, compatible clinical features, presence of granulomas, detection of beryllium in the tissues and urine and a positive patch test. Kveim tests are uniformly negative, and tuberculin tests often negative (Stoeckle *et al.* 1969). Beryllium patch tests (2% $BeSO_4$) are usually positive (Curtis 1959).

The present report is concerned with the chronic or granulomatous form of the disease.

Pathology

The characteristic hallmark of chronic beryllium disease is the sarcoid-like epithelioid cell granuloma with identical appearance in different tissues. In the lungs granulomas are found in the interstitial tissue, with a distribution similar to that in sarcoidosis. Nonspecific interstitial infiltration of histiocytes, lymphocytes and plasma cells is usually present which, together with the granulomas, contributes to progressive interstitial fibrosis, sometimes cystic change and terminal cor pulmonale. Freiman & Hardy (1970) have stressed that interstitial inflammation is associated with increased mortality.

Granulomas may also be found in other organs and in hilar lymph nodes but bilateral lymphadenopathy is unusual.

The granulomas consist of foci of epithelioid and giant cells with usually slight or absent central necrosis, together with admixture of lymphocytes and plasma cells most prominent at the periphery. Organisms are absent. Inclusion bodies, including Schaumann and asteroid bodies, may be found in both epithelioid and giant cells.

On light microscopy the morphology (Jones Williams 1958), the histochemistry (Jones Williams & Williams 1967) and the enzyme con-

Table 1
Occupations at risk

(1) Fluorescent lamps accounted for the majority of the early cases (beryllium has not been used for this purpose since 1948)
(2) Cathode tubes and X-ray machine windows
(3) Alloys: Copper, copper aluminium, copper zinc, stainless steel, nickel, chromium
(4) Ceramics
(5) Beryllium extraction from ore
(6) Experimental workers
(7) Atomic energy. Source of neutrons
(8) Neighbourhood cases: Population living 'down wind' of beryllium factories, wives of workers

tent of beryllium granulomas (Williams *et al.* 1969), together with the properties and mode of development of Schaumann bodies (Jones Williams 1960, Jones Williams & Williams 1968), are the same as in the granulomas of sarcoidosis, noncaseating tuberculosis, Crohn's disease and farmer's lung. Histochemical detection of beryllium is unsatisfactory so that pathologically the granulomas are distinguishable only by the chemical analysis of the tissue.

The nature and origin of epithelioid cells continue to be intriguing problems. Jones Williams *et al.* (1970) reported on the fine structure of these cells in sarcoidosis, Kveim reactions and tuberculosis and showed that they are again similar. The mature epithelioid cell contains numerous Golgi complexes and associated vesicles which, with our light microscopy finding of high pentose cycle enzyme activity, suggests that they are actively biosynthetic. Further work is in progress on ultrastructural histochemistry to determine the nature of the 'secretory' vesicles. They may contain lymphokines (Dumonde 1970), substances which may be responsible for features of the epithelioid cell granuloma and might prove to be the active fraction of the Kveim test.

Our morphological findings suggest a continuous progression from circulating mononuclear cells through intermediate forms to the mature epithelioid cells in the granuloma. It is probable that the circulating lymphocyte develops into a 'young' and then into a mature epithelioid cell. Giant cells show features similar to the mature epithelioid cell, supporting the common theory that they arise from fusion of the latter.

We are currently investigating the fine structure of granulomas from a case of chronic beryllium disease (*vide infra*). Our initial findings are of mature epithelioid and giant cells similar to those described above (Fig 1).

The following case illustrates many of the features of chronic beryllium disease and emphasizes the continuing risk of beryllium exposure in industry.

Case Report

This report concerns a man of 48 years who, following a relatively trivial finger injury, developed systemic chronic beryllium disease (Jones Williams *et al.* 1967). Initially, he cut his finger on a grinding wheel contaminated with beryllium oxide. This injury developed into a chronic skin ulcer which failed to respond to steroids and fifteen months later necessitated amputa-

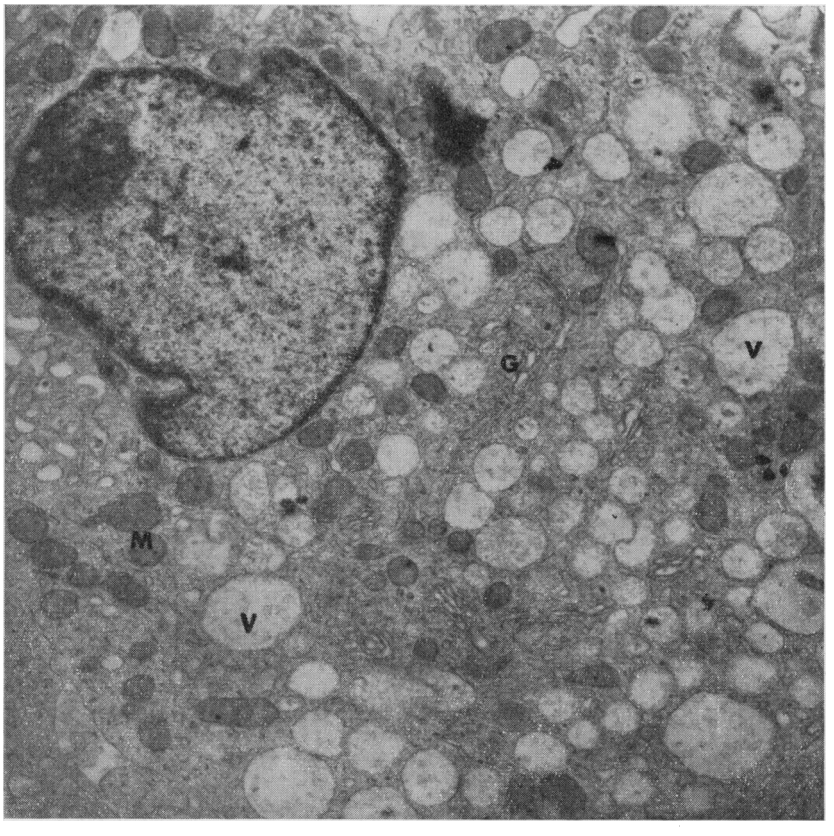

Fig 1 *Epithelioid cell.* M, *mitochondria.* G, *Golgi complex.* V, *vesicles. Uranyl acetate and lead citrate.* × *11,000*

tion of the affected finger. Noncaseating granulomas were present in the ulcer and spectroscopic analysis revealed the presence of beryllium. The diagnosis was further confirmed by a positive patch test.

Six months later, 21 months after the original injury, two granulomas together with beryllium-containing nodules were removed from the lymphatics of the same forearm. The wounds healed, chest symptoms were absent and there was no radiological evidence of disease.

The patient remained apparently well but in June 1970, nearly seven years after the original injury, he presented with multiple firm nodules along the course of the lymphatics in the injured arm. Biopsy showed fibrous nodules with surrounding epithelioid cell granulomas which on analysis contained beryllium. Of even graver import are the radiological findings of bilateral pulmonary mottling, evidence of impaired pulmonary function, and the presence of granulomas in a lung biopsy.

It is probable that the recurring lymphatic lesions resulted from the original injury, but the chest lesions indicate an additional inhalation exposure.

This case exemplifies the toxic nature and persistence of beryllium in the tissues. Though steroids failed to control the initial lesion, heavy steroid therapy appears to offer the only hope for successful treatment.

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Meeting February 8 1971

Professor J Pepys presented his Presidential Address which was entitled **Immunological Basis of Fibrosis of the Lungs**